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HUMAN AND VETERINARY DRUGS

Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 201, 207, 210, 211, 229]

[Docket No. 75N–0339]

HUMAN AND VETERINARY DRUGS

Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding

The Commissioner of Food and Drugs proposes to revise the current good manufacturing practice (CGMP) regulations for human and veterinary drugs (21 CFR Parts 210 and 211) to update them in light of current technology and to adopt more specific requirements better to assure the quality of finished drug products. Interested persons have until June 14, 1976, to submit comments.

Over the past several years the Commissioner has directed a review of the CGMP regulations. These regulations, which establish requirements for current good manufacturing practice for finished pharmaceuticals, were originally published in the FEDERAL REGISTER of June 20, 1963 (28 FR 6385) and were last substantially revised in the FEDERAL REGISTER of January 15, 1971 (36 FR 601).

In considering the revisions being proposed at this time, the Commissioner has relied on the Food and Drug Administration's (FDA) experience, gained during the last 12 years through inspectional and compliance activities and numerous discussions with the drug industry and drug trade associations at various meetings, seminars, and workshops, to provide the background and information that serve as a basis for the proposed improvements.

Another important consideration leading to this proposal came from the findings of separate studies, conducted in 1973 by the Office of Management and Budget (OMB) and the General Accounting Office (GAO), of Federal procurement of medical and nonperishable subsistence supplies. The GAO published its conclusions in a report of December 6, 1973, entitled, "How to Improve the Procurement and Supply of Drugs in the Federal Government," in which it recommended that FDA be the single Federal agency responsible for drug quality assurance. The OMB report dated January 4, 1974, entitled, "Study of an Optimum Procurement and Distribution System(s) for Medical and Non-Perishable Subsistence Items," identified duplication and inefficiency in Federal procurement of medical items. Copies of these studies have been placed on file in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852. As a result of these reports, on June 4, 1974, the OMB requested the Secretary of Health, Education, and Welfare to assume full responsibility for developing an executive branch plan to consolidate government-wide quality assurance programs for drugs. The FDA, in cooperation with the Department of Defense (DOD), Veterans Administration (VA), and Health Services Administration (HSA), has developed an executive branch plan making FDA responsible for quality assurance for all drugs and biologics purchased, stored, and distributed by the purchasing agencies. An agreement has been reached with HSA regarding the responsibility of FDA to provide quality assurance for drugs, biologics, chemicals and reagents that HSA procures, stores, and distributes.

A memorandum of understanding concerning this agreement was published in the FEDERAL REGISTER of July 8, 1975 (40 FR 28656). Also, an interagency agreement with the Veterans Administration was published in the FEDERAL REGISTER of August 22, 1975 (40 FR 36787). A similar formal agreement with DOD was published in the FEDERAL REGISTER of January 27, 1976 (41 FR 3887); thus FDA has assumed responsibility for quality assurance of all drugs, including biologics, that are procured, stored, and distributed by Federal agencies. In reviewing the need for revised CGMP regulations at this time, the Commissioner took into consideration the requirements of these Federal purchasing agencies to be certain that uniform and appropriate criteria are being proposed.

In addition to FDA's own recognition of the need for updating the CGMP regulations and the OMB request for a single CGMP standard for all drugs procured by government agencies, the Office of Technology Assessment (OTA), Congress of the United States, recently established a panel to study problems of drug bioequivalence. The panel reported that the CGMP regulations were too general and therefore may be subject to wide differences in interpretation, and that they do not insure quality and uniform bioavailability for drug products.

The Commissioner has studied the panel's recommendations extensively and finds a number of their comments pertinent to current good manufacturing practice. The proposed revisions in the regulations include several changes reflecting suggestions made by OTA. An example is the requirement that manufacturers give increased attention to statistical sampling and monitoring of intermediate production steps. These proposed regulations are not designed to provide the final assurance of the bioavailability of a drug, although the in-process and finished drug product controls proposed should contribute measurably to resolving a problem of bioavailability where identifiable manufacturing deficiencies are responsible for such a problem. The bioavailability and bioequivalence requirements for drug products have been addressed in separate FEDERAL REGISTER proposals published in the FEDERAL REGISTER of June 20, 1975 (40 FR 26157 and 26164). Until a bioavailability or bioequivalence standard is identified for a drug, quality control procedures to assure compliance with the appropriate standards cannot be established. Further CGMP requirements will be specified for drug products, either by class or for individual products, as the need is determined.

The Commissioner intends for CGMP regulations to become binding specific requirements that must be complied with; failure to do so shall render a drug product adulterated under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 701(a) of the act empowers the Commissioner to promulgate substantive rules to facilitate enforcement of the act's other provisions. "National Nutritional Foods Ass'n. v. Weinberger," 512 F. 2d 688 (2d Cir. 1975); "Weinberger v. Hynson, Westcott & Dunning, Inc.," 412 U.S. 609 (1973); "CIBA Corp. v. Weinberger," 412 U.S. 640 (1973); "Weinberger v. Bentex Pharm. Inc.," 412 U.S. 645 (1973). Publication of proposed specific regulations regarding current good manufacturing practice will allow all members of the industry an opportunity to participate in their preparation and to note the level of performance expected of them. Binding regulations will also serve to inform courts of FDA's expert judgments regarding current good manufacturing practice for drugs in the United States; this will expedite and assist enforcement proceedings to assure compliance with section 501(a)(2)(B) of the act. The legal status of the CGMP regulations is set forth in proposed § 210.1.

Because of the definitive nature of these proposed regulations, the Commissioner urges interested persons to review them carefully, to identify any areas that require clarification or modification, and to submit reasoned comments that, wherever possible, suggest precise alternative language. Ordinarily 60 days is provided for comment on a proposal, although the Commissioner can reduce or extend this time period for good cause. Because of the nature and extent of revisions being proposed, the Commissioner has concluded that 120 days should be allowed for public comment. In the absence of extraordinary circumstances, no extension of time for comment will be granted.

The Commissioner emphasizes that, although some of the proposed revisions represent requirements not specifically included in the existing CGMP regulations, in many instances such revisions are practices that have been considered implicit in the regulations or are at least considered by most manufacturers to be desirable requirements for their own operations. Where significant new requirements are being proposed, a detailed discussion of them will appear in this preamble. The new proposed format for the CGMP regulations will provide the user with requirements that are easier to locate and to read. The proposed format will also provide the necessary expansion needed for future CGMP regulations for specific classes of drugs or manufacturing processes.

To aid the reader, the following table is provided to show the relationship of the proposed CGMP regulations to existing ones under the 1974 Code of Federal Regulations (Part 133) designation and the 1975 recodification designation published in the FEDERAL REGISTER of March 27, 1975 (40 FR 14024). The reader is encouraged to make a line-by-line comparison of the revised sections with the existing CGMP regulations to identify every proposed change.

Proposed	Mar. 27, 1975, recodification	1974 Code of Federal Regulations	Nature of text change
210.1(a)	211.1(a)	133.2(a)	Revised.
210.1(b)	211.1(a)	133.2(a)	Do.
210.2	New	New	New.
210.3(b)(1)	210.3(a)	133.1(a)	Revised.
210.3(b)(2)	210.3(d)(2)	133.1(d)(2)	No change.
210.3(b)(3)	210.3(d)(1)	133.1(d)(1)	Revised.
210.3(b)(4)	New	New	New.
210.3(b)(5)	211.40(j)(1)	133.8(j)(1)	Revised.
210.3(b)(6)	211.40(f)(1)	133.8(j)(1)	Do.
210.3(b)(7)	210.3(d)(5)	133.1(d)(5)	Do.
210.3(b)(8)	210.3(d)(6)	133.1(d)(6)	Do.
210.3(b)(9)	New	New	New.
210.3(b)(10)	210.3(d)(3)	133.1(d)(3)	Revised.
210.3(b)(11)	210.3(d)(4)	131.1(d)(4)	Do.
210.3(b)(12)	New	New	New.
210.3(b)(13)	210.3(c)(1)	133.1(c)(1)	Revised.
210.3(b)(14)	210.3(c)(2)	133.1(c)(2)	Do.
210.3(b)(15)	210.3(d)(7)	133.1(d)(7)	Do.
210.3(b)(16)	210.3(d)(8)	133.1(d)(8)	Do.
210.3(b)(17)	New	New	New.
210.3(b)(18)	New	New	New.
210.3(b)(19)	New	New	New.
210.3(b)(20)	210.3(b)	133.1(b)	Revised.
210.3(b)(21)–(24)	New	New	New.
211.1(a)	New	New	New.
211.1(b)	New	New	New.
211.2(a)	211.1(b)	133.2(b)	Revised.
211.2(b)	211.1(b)	133.2(b)	Do.
211.3	New	New	New.
211.22 (a)–(d)	New	New	New.
211.25 (a)–(c)	211.10(a)	133.5(a)	Revised.
211.28 (a)–(c)	New	New	New.
211.28(d)	211.10(b)	133.5(b)	Revised.
211.34	New	New	New.
211.42(a)	211.20	133.3	Revised.
211.42(b)	211.20(a)(1)	133.3(a)(1)	Do.
211.42(c)	New	New	New.
211.42(c)(1)	211.20(a)(2)	133.3(a)(2)	Revised.
211.42(c)(2)	211.20(a)(3)	133.3(a)(3)	Do.
211.42(c)(3)	211.20(a)(4)	133.3(a)(4)	Do.
211.42(c)(4)	New	New	New.
211.42(c)(5)	211.20(a)(5)	133.3(a)(5)	No change.
211.42(c)(6)	211.20(a)(6)	133.3(a)(6)	Do.
211.42(c)(7)	211.20(a)(7)	133.3(a)(7)	Revised.
211.42(c)(8)	211.20(a)(7)	133.3(a)(7)	Do.
211.42(c)(9)	211.20(a)(8)	133.3(a)(8)	Do.
211.42(c)(10)	New	New	New.
211.42(d)	New	New	New.
211.44	211.20(b)	133.3(b)	Revised.
211.46(a)	211.20(b)	133.3(b)	Do.
211.46(b)	211.20(b)	133.3(b)	Do.
211.46 (c)–(e)	New	New	New.
211.48(a)	211.20(d)	133.3(d)	Revised.
211.48(b)	211.20(d)	133.3(d)	Do.
211.50	211.20(f)	133.3(f)	Do.
211.52	211.20(e)	133.3(e)	Do.
211.54	211.20(e)	133.3(e)	Do.
211.56 (a)–(d)	New	New	New.
211.58	New	New	New.
211.63	211.30	133.4	Revised.
211.65(a)	211.30(a)	133.4(a)	Do.
211.65(b)	211.30(b)	133.4(b)	Do.
211.67(a)	211.30	133.4	Do.
211.67(b)	New	New	New.
211.67(c)	New	New	New.
211.68(a)	211.1(b)	133.2(b)	Revised.
211.68(b)	New	New	New.
211.72(a)	211.40(j)(1)	133.8(j)(1)	Revised.
211.72(b)	211.40(j)(2)	133.8(j)(2)	Do.
211.72(c)	211.40(j)(3)	133.8(j)(3)	Do.
211.80(a)	New	New	New.
211.80(b)	211.42(f)(1)	133.6(f)(1)	Revised.
211.80(c)	New	New	New.
211.80(d)	211.42	133.6	Revised.
211.82(a)	211.42(a)	133.6(a)	Do.
211.92(b)	New	New	New.
211.84(a)	211.42	133.6	Revised.
211.84(b)	New	New	New.
211.84(c) (1)–(6)	New	New	New.
211.84(d) (1)–(3)	New	New	New.
211.84(d)(4)	211.42(c)	133.6(c)	Revised.
211.84(d)(5)	211.42(e)	133.6(e)	Do.
211.84(e)	New	New	New.
211.86	211.42(f)(2)	133.6(f)(2)	Revised.
211.87	211.42(f)	133.6(f)	Do.
211.88	211.42(f)	133.6(f)	Do.
211.89	211.42(f)(3)	133.6(f)(3)	Do.
211.94(a)	211.55	133.9	Do.
211.94(b)	211.55	133.9	Do.
211.94(c)	211.55	133.9	Do.
211.94(d)	New	New	New.
211.94(e)	New	New	New.
211.96	New	New	New.
211.100(a)	New	New	New.
211.100(b)	New	New	New.
211.101	New	New	New.
211.101(a)	New	New	New.
211.101(b)	New	New	New.
211.101 (c)–(d)	211.40(a)	133.8(a)	Revised.
211.102	New	New	New.
211.103	211.40(a)	133.8(a)	Revised.
211.105(a)	211.40(b)	133.8(b)	Do.
211.105(b)	New	New	New.
211.110(a)	211.40(f)	133.8(f)	Revised.
211.110(b)	New	New	New.
211.111	New	New	New.

Proposed	Mar. 27, 1975, recodification	1974 Code of Federal Regulations	Nature of text change
211.112(a)	211.40(e)	133.8(e)	Revised.
211.112(b)	211.40(e)	133.8(e)	Do.
211.113(a)	211.40(f)	133.8(d)	Do.
211.113(b)	211.40(d)	133.8(d)	Do.
211.115(a)	211.40(f)	133.8(d)	Do.
211.115(b)	New	New	New.
211.122(a)	211.80(c)(1)	133.10(c)(1)	Revised.
211.122(b)	211.80(c)(1)	133.10(c)(1)	Do.
211.122(c)	New	New	New.
211.122(d)	211.80(c) (2) and (4)	133.10(c) (2) and (4)	Revised.
211.122(e)	211.80(c)(3)	133.10(c)(3)	Do.
211.122(f)	211.80(c)(5)	133.10(c)(5)	Do.
211.122(g)	New	New	New.
211.125 (a)–(d)	211.80(d)	133.10(d)	Revised.
211.125(e)	New	New	New.
211.125(f)	211.80(d)	133.10(d)	Revised.
211.125(g)	New	New	New.
211.130	211.80	133.10	Revised.
211.130(a)	211.80(a)	133.10(a)	Do.
211.130(b)	211.80	133.10	Do.
211.130(c)	211.80	133.10	Do.
211.130(d)	211.80	133.10	Do.
211.130(e)	211.80(b)	133.10(b)	Do.
211.130(f)	New	New	New.
211.134(a)	New	New	New.
211.134(b)	211.80(e)	133.10(c)	Revised.
211.134(c)	New	New	New.
211.137(a)	211.62	133.14	Revised.
211.137(b)	211.62(a)	133.14(a)	Do.
211.137(c)	211.62(b)	133.14(b)	Do.
211.137(d)	211.62(c)	133.14(c)	Do.
211.137(e)	New	New	New.
211.142	New	New	New.
211.142(a)	New	New	New.
211.142(b)	New	New	New.
211.150	New	New	New.
211.150(a)	211.110(b)	133.12(b)	Revised.
211.150(b)	211.110(a)	133.12(a)	Do.
211.160(a)	New	New	New.
211.160(b)	211.58	133.11	Revised.
211.160(b)(1)	211.58(a)	133.11(a)	Do.
211.160(b)(2)	211.58(c)	133.11(c)	Do.
211.160(b)(3)	211.58(d)	133.11(d)	Do.
211.160(b)(4)	New	New	New.
211.165(a)	211.58(e)	133.11(e)	Revised.
211.165(b)	211.58(e)(1)	133.11(e)(1)	Do.
211.165(c)	New	New	New.
211.165(d)	New	New	New.
211.165(e)	New	New	New.
211.165(f)	211.58(f)	133.11(f)	Revised.
211.165(g)	New	New	New.
211.166(a)	New	New	New.
211.166(a) (1)–(2)	New	New	New.
211.166(a)(3)	211.60(a)	133.13(a)	Revised.
211.166(a)(4)	211.60(b)	133.13(b)	Do.
211.166(a)(5)	211.60(c)	133.13(c)	Do.
211.166(b)	211.60(d)	133.13(d)	Do.
211.167(a)	211.58(e) (1)–(2)	133.11(e) (1)–(2	Do.
211.167(b)	211.58(e)(3)	133.11(e)(3)	Do.
211.167(c)	211.58(e)(4)	133.11(e)(4)	Do.
211.170(a)	211.42(h)	133.6(h)	Do.
211.170(b)	211.58(g)	133.11(g)	Do.
211.173	211.58(f)	133.11(f)	Do.
211.176	211.58(j)	133.11(j)	Do.
211.180(a)	211.101(b)	133.7(b), 133.11(h), and 133.12 (a).	Do.
211.180(b)	New	New	New.
211.180(c)	New	New	New.
211.180(d)	New	New	New.
211.180(e)	New	New	New.
211.182	New	New	New.
211.184(a)	211.42(g)(1)	133.6(g)(1)	Revised.
211.184(b)	211.42(g)(2)	133.6(g)(2)	Do.
211.184(c)	211.42(g)(3)	133.6(g)(3)	Do.
211.184(d)	New	New	New.
211.186(a)	211.101(a)	133.7(a)	Revised.
211.186(b)(1)	211.101(a)(1)	133.7(a)(1)	Do.
211.186(b)(2)	211.101(a)(2)	133.7(a)(2)	Do.
211.186(b) (3)–(7)	211.101(a)(3)	133.7(a)(3)	Do.
211.186(b)(8)	211.101(a)(4)	133.7(a)(4)	Do.
211.186(b)(9)	211.101(a)(5)	133.7(a)(5)	Do.
211.188	211.101(b)	133.7(b)	Do.
211.188(a)	211.101(b)(1)	133.7(b)(1)	Do.
211.188(b) (1)–(5)	211.101(b)(2)	133.7(b)(2)	Revised.
211.188(b) (6)–(10)	New	New	New.
211.188(b)(11)	211.101(b)(2)	133.7(b)(2)	Revised.
211.188(b)(12)	211.101(b)(4)	133.7(b)(4)	Do.
211.188(b)(13)	New	New	New.
211.192	211.40(h)	133.8(h)	Revised.
211.194(a) (1)–(9)	New	New	New.
211.194 (b)–(d)	New	New	New.
211.196	211.110(a)	133.12(a)	Revised.
211.198(a)	211.115	133.15	Do.
211.198(b)	211.115	133.15	Do.
211.204	211.40(l)	133.8(l)	Do.
211.206	New	New	New.
Deleted	210.3(d)(8)(ii)	133.1(d)(8)(ii)	Deleted.

A number of the revisions constitute new or expanded requirements. As discussed earlier, the Commissioner believes that many of these requirements are already a part of most manufacturers' operations. Other requirements may be new to many firms, but are necessary to assure drug product quality. Changes proposed in the existing CGMP regulations include the following:

DEFINITIONS

1. In proposed § 210.3 the statutory references have been updated.

2. In proposed § 210.3(b)(4) "drug product" has been defined. This term is used and defined in the proposed Bioavailability and Bioequivalence Requirements published in the FEDERAL REGISTER of June 20, 1975 (40 FR 26164). To assure consistency of use, the term is also defined here.

3. In proposed § 210.3(b)(9) "in-process materials" has been defined.

4. In proposed § 210.3(b)(10) "lot" has been redefined to remove any reference to lot number.

5. In proposed § 210.3(b)(11) "lot number," "control number," or "batch number" have been defined.

6. In proposed § 210.3(b)(12) a paragraph has been added to define "manufacture, processing, packing, or holding of a drug product." This change provides for consistency throughout the CGMP regulations.

7. In proposed § 210.3(b)(15) "materials approval unit" has been replaced by "quality control unit" and redefined. The latter term appears to be of more common usage in the industry.

8. In proposed § 210.3(b) (17), (18), and (19) "theoretical yield," "actual yield," and "percentage of theoretical yield" have been defined.

9. In proposed § 210.3(b) (21), (22), (23), and (24) "acceptance criteria," "acceptable quality level (AQL)," "unacceptable quality level (UQL)," and "representative sample," which relate specifically to statistical evaluation, have been defined.

GENERAL PROVISIONS

1. Proposed § 211.1(b) clarifies the applicability of the CGMP regulations to all drug products and provides that where other requirements appear elsewhere in the regulations, the more specific provisions shall apply over the more general. The Commissioner intends to propose at future times CGMP regulations for specific classes of drug products such as large volume parenterals, medical gases, and radiopharmaceuticals, and regulations for certain kinds of manufacturing activities such as the manufacturing of bulk drug components, repacking, or relabeling.

2. Proposed § 211.2(b) permits the use of computers in the manufacture, processing, packing, and holding of drug products, with a requirement that hard copy backup files be maintained of computerized records and that changes in those records be made only by authorized personnel.

ORGANIZATION AND PERSONNEL

1. Proposed § 211.22 clarifies the requirement for a quality control unit and outlines its responsibilities, including authority for approving or rejecting components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products. This does not, however, relieve other units from the responsibility of verifying and reviewing the correctness of their own work.

Also, this proposed section requires that adequate laboratory facilities be available to the quality control unit. This requirement is designed to assure that the quality control unit will have necessary access to laboratory facilities, when needed, to perform their quality control functions.

2. Proposed § 211.25 is designed to assure that each employee involved in drug manufacturing and control is properly trained and familiar with the CGMP regulations as they relate to his functions. Many manufacturers already have such programs of instruction. The attitude and approach to training that a manufacturer presents to employees reflect his view of the importance of CGMP regulations and determine the degree to which the employee will consider it necessary to conform to standard operating procedures. The emphasis on CGMP regulations through regularly conducted training or through formal courses, either on the premises or at another location, should result in more appreciation and understanding of the responsibility and importance of the employee's role. The extent and frequency of training needed will depend on the scope of the employee's activities and experience. However, there are times when instruction would be needed such as orientation for new employee or employees engaging in new activities, when new company or drug standards have been adopted or revisions in the CGMP regulations have been published, and when new equipment or a new process is to be used.

3. Proposed § 211.28 includes specific requirements for employee garb and work habits. For example, it requires covering the hair on the head and face when necessary to prevent drug contamination. This section specifically states that only authorized personnel shall enter limited-access areas.

4. Proposed § 211.34 specifically requires that consultants have sufficient education and experience to advise on the subject for which they are retained and that records be maintained that state the consultant's name, address, qualifications, and the type of consulting service he provides for a drug firm. Consultants have not been mentioned previously in the CGMP regulations, but FDA's interpretation of the personnel requirements has always been that consultants must be appropriately qualified.

BUILDINGS AND FACILITIES

1. In proposed § 211.42(b) and in a number of other paragraphs, the word "prevent" has replaced the word "minimize." The Commissioner finds that the requirement to "minimize" the risk of creating a particular undesirable condition has not conveyed, in the past, the intention of the FDA and has resulted in confusion as to what must be accomplished. The purpose of requiring the orderly placement of equipment and materials, for example, is to "prevent" a situation or condition in which the placement could contribute to mixups between different drugs or different labeling.

2. In proposed § 211.42(c) a new requirement has been added to specify that an aseptic processing area be provided when appropriate for the type of operations performed by the manufacturer. The current regulations require that, generally, adequate space be provided for manufacturing and control functions. The Commissioner believes this requirement must be updated to require separate areas for quarantining unreleased raw materials and materials at other specific stages of use.

3. Proposed § 211.42(d) requires that penicillin operations be performed in facilities separate from those used for non-penicillin drug products. Current regulations do not require this. Based on FDA experience, the Commissioner finds that where common equipment or facilities are used for drug production, there is likely to be contamination of non-penicillin drug products with penicillin. While some of these contaminated drug products are within the current allowable tolerance for penicillin contamination, the Commissioner proposes in § 211.176, discussed later in this preamble, to delete the allowable tolerance for penicillin cross-contamination of non-penicillin-containing drugs. The Commissioner finds that the current good manufacturing practice in the industry has, to a large extent, eliminated penicillin cross-contamination by producing penicillin products in a separate building or a separate area that has an air-handling system independent of other production areas, and is effectively sealed off from other parts of the building to prevent contamination of areas handling non-penicillin products.

4. In proposed § 211.46, new, more specific requirements are included for in-plant air filtration systems to improve air quality in production areas and reduce the potential for air-borne contamination. While high efficiency particulate air filters are certainly necessary for aseptic processing areas, and would be desirable in any manufacturing situation, this section does not require such filters in a non-sterile processing area.

5. Proposed § 211.56 is a new section entitled "Sanitation." It expands on the previous requirements for sanitation, including specific prohibitions against misusing insecticides and rodenticides, and it requires a written sanitation program.

The proposed revision in this section and in a number of other sections of the CGMP regulations (§§ 211.22, 211.56, 211.67, 211.80, 211.94, 211.100, 211.101,

211.110, 211.112, 211.113, 211.115, 211.122, 211.125, 211.130, 211.142, 211.150, 211.160, 211.165, 211.166, 211.167, 211.186) includes a requirement for written procedures to describe specific manufacturing and control operations. This requirement will provide additional assurance for reliable continuation of a firm's established policies and procedures and will assure that appropriate information is conveyed from management to production line personnel. Written procedures, frequently termed "standard operating procedures," are already a part of the daily operations of many firms. The essence of good standard operating procedures is not only that the procedures themselves are adequate to assure drug product quality but that they are available to, and understood by, all persons to whom they are intended to apply. The substantive requirements in these CGMP regulations should be considered as a basis for standard operating procedures.

EQUIPMENT

Proposed § 211.68 is another of the many new sections that formalizes a practice that has long been considered current good manufacturing practice—in this case, the periodic calibration of scales and balances, with written documentation of semiannual calibration checks.

CONTROL OF COMPONENTS, DRUG PRODUCT CONTAINERS, CLOSURES AND IN-PROCESS MATERIALS

1. Proposed § 211.80 includes a number of revisions. Many are already part of most manufacturers' operations, either because they are understood to be part of the existing CGMP regulations or because they are logical extensions of the existing requirements. The basic concept in this section is to assure that only the correct component, drug product container, and closure is received and used by the manufacturer. To accomplish this, the manufacturer must take certain precautions to prevent improper components, drug product containers, and closures from becoming a part of the inventory system. Proper examination, including testing, where appropriate, of components, in-process materials, drug product containers, and closures, and proper control of these materials throughout their use, will provide added confidence in the drug product. Specific revisions include:

a. In proposed § 211.80(a) a specific requirement is added for written procedures to be established and followed for the control of components, drug product containers, and closures.

b. Proposed § 211.80(d) requires that an identifying code be assigned and used for containers of components, drug product containers, and closures in order to provide a system for monitoring their disposition.

2. Proposed § 211.82(a) is reworded to clarify that the receiving firm shall visually examine the container of each component, drug product container, and closure upon receipt and before acceptance.

3. In proposed § 211.82(b) the requirement for a quarantine area for untested and unreleased components, drug product containers, and closures is unequivocally stated here and supports § 211.42 (c), which requires separate areas for certain manufacturing and control functions.

4. Proposed § 211.84 (b) and (c) deal with a new set of requirements that include specific controls to assure that representative samples are collected and that contamination during the act of sampling is unlikely. Representative samples are to be collected at random following a sampling schedule based on appropriate statistical criteria.

5. Proposed § 211.84(d) (2) extends the requirement for testing components for conformance to specifications to include all ingredients, both active and inactive. In lieu of such testing, the supplier's report of analysis will be accepted under stated specified conditions.

PRODUCTION AND PROCESS CONTROLS

1. In proposed § 211.101 a series of requirements are specified for identifying component containers after the material is removed from the original bulk containers, and for weighing components for dispensing to manufacturing. Specifically, the proposed regulation clarifies the information that must appear on component containers for dispensing to manufacturing. There is a requirement to examine component containers dispensed to manufacturing to assure that the component is properly released for use, the weight or measure is correct, and the containers are properly identified as outlined in this section. Also, the Commissioner proposes to formalize a long-standing policy of FDA and most drug manufacturers to require each batch to be formulated with the intent to provide not less than 100 percent of the labeled amount of the active ingredient.

2. Proposed § 211.105(b) includes a minor revision intended to clarify that it is only major equipment used during production that must be identified. This revision does not change the intent of the existing CGMP regulations but merely recognizes the impracticality of identifying every piece of equipment used during a production period, as, for example, portable equipment such as hand-held implements.

3. Proposed §§ 211.110 and 211.165(d) include revisions to specify acceptable procedures for sampling and testing. FDA recognizes that there may be variability for a given attribute between different classes of drugs, between similar drug products of different manufacturers, and even between different dosage units of the same drug product from a single manufacturing cycle. Therefore, no single sampling and acceptance plan may be adequate for a firm's entire production. No sampling plan for components, in-process materials, or drug products can assure complete freedom from the risk of accepting a batch of the drug product that contains some units not meeting established chemical or physical specifications. It is possible, however, through appropriate application of statistical methodology, to devise sampling plans that will provide a high probability that lots with unacceptable percentages of defective units in components, in-process materials, or drug products will be rejected.

For in-process material, and for the drug product during production, the proposal requires that valid in-process specifications for appropriate characteristics be established. Such in-process specifications shall be consistent with established specifications for the finished drug product and shall be derived from previous acceptable process average and process variability estimates determined by the application of suitable statistical procedures. Examination and testing of samples taken during production shall be adequate to assure that the drug product and in-process materials conform to appropriate in-process specifications.

The proposal further requires that acceptance criteria that include appropriate specifications and statistical quality control criteria be developed for each drug product. Statistical quality control criteria, including an Acceptable Quality Level (AQL) and an Unacceptable Quality Level (UQL), shall be assigned to specifications that require multiple examination or testing of dosage units such as the weight variation, content uniformity, disintegration, and dissolution of drug products. Manufacturers will be required to establish sampling and testing procedures to assure that there is no greater than a 5 percent probability of acceptance for batches whose percent of defective units exceeds the UQL for each appropriate characteristic. For those product quality characteristics requiring multiple testing and examination, this requirement may be satisfied through the utilization of drug product testing, statistical quality control data developed and recorded during the processing of the batch, and statistical data derived from validation studies conducted to determine the variability of the manufacturing processes. The establishment of an AQL and UQL is not required for testing procedures for characteristics such as batch potency (which is based on a composite sample), identification, and pH, where a single determination is a requirement and in-process procedures are properly validated and controlled. Although statistical quality assurance is relatively new to some manufacturers, these procedures are currently used by many manufactuers as a basis for the sampling and acceptance of components, in-process materials, and drug products.

FDA recognizes that there are differing conceptual and statistical approaches to the general problem of estimating with a high probability of correctness the extent to which individual units in a given batch meet all appropriate specifications. The agency also recognizes that careful attention both to in-process controls and testing and to end-product testing is

necessary for adequate quality assurance and believes that regulations requiring such controls and testing are appropriate. Articulating such requirements, however, has proven to be a difficult problem in drafting these proposed regulations, and controversy over the approach and language proposed herein is anticipated. The Commissioner reemphasizes that the intent of the good manufacturing practice regulations is to provide clear, unambiguous standards that are scientifically appropriate, necessary for assurance of the quality of drug products, and enforceable. He specifically requests all interested persons to review this section of the regulations to assure that the proposed regulations meet these important objectives. He also requests that those who disagree with this proposed section, and/or the corresponding definitions, provide not only their criticisms but also reasoned alternative approaches and clear alternative language.

4. Proposed § 211.111 requires that, when appropriate, time limits for the completion of each stage of production be established so that the quality of the drug product is not reduced. It is well recognized that the in-process time of particular drug products can create certain manufacturing difficulties. For example, there may be problems associated with processes used for the production of sterile products, drug products containing hygroscopic ingredients, and drug products containing highly volatile components. Manufacturers must establish procedures to eliminate any undue delays in the production of products susceptible to a quality reduction as a result of processing time.

PACKAGING AND LABELING CONTROL

1. In proposed § 211.122 the general requirements for labeling include specific reference to all packaging materials rather than just to the labels. Because mixups in packaging materials can affect the identity or integrity of the packaged drug product, all packaging materials must be controlled to assure that only the correct materials are used. This section also requires storage of labels for different products, strengths, dosage forms, and quantity of contents in separate compartments and requires control over on-line printing devices.

2. Proposed § 211.125(c) expands the former requirement for reconciling labels issued and used; it includes a requirement that any labels returned to label storage be reconciled.

3. Proposed § 211.125(e) requires control over labels returned to storage after a packaging and labeling operation to prevent mixups.

4. Proposed § 211.130(f) requires removal of packaging and labeling materials from the finishing areas after completion of operations to prevent mixups with subsequent operations.

5. Proposed § 211.134(a) requires the examination of packaged and labeled drug products during finishing operations to provide assurance that every container and package in a lot has the correct labeling. The Commissioner finds that most recalls involving packaging or labeling operation deficiencies could have been avoided if each drug product container and package had been adequately examined for the correct label and for the proper container in the package carton. The examination of drug products may be mechanical, electronic, or visual.

6. In proposed § 211.137 the expiration dating is revised to require expiration dating for all drug products. Consumers of pharmaceuticals have a vital interest in having those products maintain the identity, strength, quality, and purity essential to render them safe and effective for use. The stability of a drug product during the period of time between its manufacture and its delivery to the patient can have a major influence on such identity, strength, quality, and purity. Many factors affect drug product stability. These include the stability of the active ingredients, the interaction of active and inactive ingredients, the manufacturing process, the storage conditions, the dosage form, the container closure system, the conditions under which the drug product is shipped, stored, and handled by wholesalers and retailers, and the length of time between initial manufacture and final use. Although some of these factors are not within the direct control of the manufacturer, the use of expiration dating by the manufacturer will encourage the removal of outdated or aged stocks.

This matter was the subject of a conference on dating pharmaceuticals held in 1965 at the University of Wisconsin. (The proceedings were published in 1970; a copy has been placed on display in the office of the Hearing Clerk, Food and Drug Administration.) At the conference, a number of papers were presented regarding various aspects of drug expiration dating, including criteria and methods for statistically validating expiration dates and actual experiences of drug manufacturers regarding current drug dating programs. At that time, several drug manufacturers had concluded that drug expiration dating for all pharmaceuticals is desirable, and voluntary expiration dating for all their drug products had been initiated. Several major pharmaceutical manufacturers suggested that a 5-year dating period would be appropriate, based on their experiences with respect to the period of time drug products are likely to remain in the distribution system, and as an approximate endpoint at which they feel a replacement of the aged stock should be made.

Many drug products, such as antibiotics, biologics, and drugs liable to deterioration, already are required to bear expiration dates based on appropriate stability studies. In addition, the "United States Pharmacopeia" (USP), XIX, at page 9, and the "National Formulary" (NF), XIV, at page 17, require, in the absence of a specific requirement in the individual monograph for a dosage form, that the label bear an expiration date assigned for the particular formulation and package of the article. Originally the effective date for this requirement was July 1, 1975. However, the USP Convention, Inc., in the First Interim Revision Announcement pertaining to USP XIX and NF XIV, deferred the effective date of that requirement to January 1, 1976. Also, as previously mentioned, a number of manufacturers are voluntarily establishing expiration dating for most or all of their drug products.

Therefore, to assure that a drug product meets its standards at the time of use, the Commissioner proposes to extend the requirement for expiration dating to all drug products. Because of the many factors affecting drug stability, the appropriate expiration date for each drug product must be determined by suitable stability studies. While an arbitrary expiration date of 5 years for those drug products not requiring a shorter period has been adopted by a number of drug manufacturers, the Commissioner does not have sufficient information at this time to conclude that setting a specific maximum expiration dating period is suitable or even desirable for all drug establishments and for all drug products. Further, there is little data to support the view that the individual consumer will be better served by a maximum expiration date such as 5 years, compared to a longer expiration date that is fully supported by stability data for the specific drug product. Recognizing the interest of some manufacturers in a specific, if arbitrary, maximum expiration dating period because of the apparent marketing advantages, the Commissioner requests information and data showing that the establishment of an arbitrary date (5 years or any other time period) is in the interest of the consumer. The regulation, as proposed in § 211.137, would in no way prohibit individual drug firms from adopting a uniform maximum 5-year dating period for their own drug products, provided stability data demonstrates that the 5-year dating period is valid. Also, the proposed regulation would not prohibit individual drug firms from extending the expiration date for their own drug products at any time prior to the original expiration date. However, any extension of an expiration date must be fully supported by stability data for the specific drug product, and the labeling thereon must be revised to comply with the requirements of § 201.17 (21 CFR 201.17).

Because of the addition of proposed § 211.137, it has been necessary to propose a revision of § 201.17 of the labeling regulations. Proposed § 201.17 requires that the expiration date of a drug product appear on the immediate drug product container, the outer retail package labeling, and the shipping carton. However, when single-dose containers are packed in individual cartons, the expiration date may properly appear on such cartons rather than on the immediate drug product containers.

HOLDING AND DISTRIBUTION

1. Proposed § 211.142 establishes minimum storage requirements for drug products before and after release for distribution by the quality control unit.

2. Proposed § 211.150 is revised to require a written procedure by which distribution of each lot of a drug product can be determined.

LABORATORY CONTROLS

1. Proposed § 211.160 requires that laboratory controls include the establishment of scientifically sound and appropriate specifications, standards, and test procedures to assure that components, drug product containers, closures, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity.

2. Proposed § 211.165(f) requires that laboratory reference standards be properly stored and tested to assure their conformance to appropriate specifications. They must be properly identified and retested when necessary. Although this requirement has always been considered current good manufacturing practice, it was not previously explicit in the regulations.

3. In proposed § 211.170 a reserve sample of essentially all components is required. Previously, only reserve samples of active ingredients were required. Any ingredient, even though not pharmacologically active, may affect the drug product and should be retained for any necessary followup investigation. Samples of components such as solvents that do not appear in the finished dosage form, compressed gases, and water need not be retained.

4. Proposed § 211.176 revises the regulations to delete any allowance for penicillin contamination of non-penicillin products. The tolerance for penicillin contamination was based on evidence of cross-contamination of drug products in plants where penicillin products were manufactured using common facilities and equipment and on the public health hazard that this presented. A review of the data for non-penicillin drug products for the past several years indicates that almost all of the samples analyzed have been free from penicillin contamination. Based on these data, the Commissioner concludes that penicillin cross-contamination is completely avoidable by practical manufacturing means.

RECORDS AND REPORTS

1. Proposed § 211.180(a), which covers all production, control, and distribution records, specifies that all records required by the regulations that are batch-related must be retained for at least 2 years after the expirtation date of the batch.

2. Proposed § 211.180(c) requires that all records or copies of such records under Subpart I of the proposal be available for inspection during the retention period at the establishment where the activities described in such records occurred. The Commissioner concludes that there is a need for this requirement since FDA has experienced some difficulty in obtaining and reviewing records that were not kept at the manufacturing site. This includes manufacturing and control records, distribution records, and complaint files.

3. Proposed § 211.180(d) provides that certain information required to be maintained by manufacturers be compiled and evaluated on a regular basis. The Commissioner recognizes that most manufacturers periodically review historical data such as production, quality control, and analytical data, as well as complaint and distribution records, to identify product variance and to update quality standards. Since this kind of drug product data analysis is being accomplished in various ways, the Commissioner proposes that a summary of such information and evaluation be prepared and maintained for review at least annually by the manufacturer. Such information shall be available for review by FDA during establishment inspections.

4. Proposed § 211.180(e) requires that procedures be established to assure that responsible corporate officials of a firm are notified in writing of possible drug product defects and other CGMP-related matters such as reports of inspectional observations issued by FDA and regulatory actions. The Commissioner finds it essential for appropriate responsible management personnel to be aware of possible failures of drug products to meet established specifications.

5. Proposed § 211.182 requires that equipment logs chronologically documenting the use and cleaning of the equipment be maintained. The Commissioner finds that this practice has been extremely useful in quickly identifying batches that need to be investigated to determine the extent of a mixup or other problem. Maintaining this log is considered a good manufacturing practice and is therefore required in these proposed regulations.

6. Proposed § 211.184(a) expands the existing requirements for component records to include more information regarding the component and the name and location of the prime manufacturer of the component, if different from the supplier, and if known.

7. Proposed § 211.184(d) requires documentation of inspection of labeling materials. Currently, documentation is not specifically required in the regulations.

8. Proposed § 211.186(a) deletes the requirement that the master production and control records be initialed and instead requires that such records contain the full signature, handwritten. The Commissioner finds that a requirement for a handwritten full signature, rather than initials as currently required, will add emphasis to the importance of this procedure and will permit ready identification of those persons who have performed such duties.

9. Proposed § 211.186(b)(7) requires manufacturers to establish tolerances for deviation from the theoretical yield and to investigate any deviation exceeding the tolerance.

10. Proposed § 211.188(b) specifies certain information that must be a part of the batch production and control records. Required information being proposed includes: (1) Proof that the packaging and labeling area was inspected before and after use; (2) a statement of percentage of theoretical yield at all major stages of processing; (3) labeling control records, including labeling specimens; and (4) any sampling performed.

11. Proposed § 211.194 specifies those records that are to be maintained in documenting the work performed in the laboratory. While there has always been a requirement that complete laboratory records be maintained on each batch of drug produced, there are other data generated by the laboratory that are not batch-related and that need to be recorded and maintained. Furthermore, the revision more precisely defines specific information generated by the laboratory (both batch-related and non-batch-related) that must be retained so that laboratory operations are documented and can thereby be considered complete. The Commissioner finds that the recordkeeping requirements proposed in the revision currently are being widely practiced in the drug industry. Additionally, the Commissioner wishes to identify the basic laboratory data that are of primary importance. This parallels the identification of basic production operations that previously have been indicated in the CGMP regulations. The Commissioner believes that such statements of specific requirements are of particular importance to firms that provide ancillary services to drug manufacturers. In this proposal, laboratory records are required to contain, among other things, the following data:

a. The source, quantity, and identity of the sample received for testing.

b. The identity of the methods used in each analysis or test, including any modification thereof.

c. The amount of sample used in each analysis or test.

d. The data obtained during each analysis or test.

e. All calculations performed in connection with each analysis or test.

f. A full explanation of, and justification for, any modification of established methods of assay.

g. The results of each analysis or test performed.

h. The identity of the persons performing and reviewing each test, and related data including the date each was performed.

12. Proposed § 211.198 specifies more clearly how complaints regarding drug products are to be handled. The Commissioner recognizes that it is not possible to foresee and identify every possible type of complaint that could be made regarding a drug product. Many complaints may involve a possible product defect and will require an investigation with laboratory testing. Other complaints may require followup by medical professionals. For still others, neither laboratory nor medical investigation may be appropriate. Therefore, the Commissioner proposes to require that all written and oral complaints be reviewed and that a determination be made whether an investigation is necessary. In the case of a

possible failure of a drug product to meet any of its specifications, an investigation under the procedures described in § 211.192 is required. Written records of the investigation are required, and where an evaluation of the complaint results in a decision that no investigation is necessary, the records must show the reason and the name of the person making that determination.

RETURNED AND SALVAGED DRUG PRODUCTS

Proposed § 211.208 was previously proposed in the FEDERAL REGISTER of January 16, 1975 (40 FR 2822). This proposal also included a revision of paragraph (b) and the addition of a new paragraph (k) to § 207.3 in Subpart A of Part 207 (21 CFR Part 207) and a revision of paragraph (a) of § 207.20 in Subpart B of Part 207. The 27 comments received regarding that proposal are currently under review. The Commissioner has concluded that this proposal should be reproposed herein, with minor revisions in order that interested persons may comment in light of the revision of the entire CGMP regulations. The Commissioner will reply to those comments already received on the January 16, 1975 proposal at the time the final regulation on this proposed revision of the CGMP regulations is published in the FEDERAL REGISTER. There is no need to resubmit comments already filed.

In reviewing the CGMP regulations, the Commissioner finds that § 229.25 is no longer necessary because of amendments to section 351 of the Public Health Service Act on October 30, 1970 (Pub. L. 91–515, 84 Stat. 1308 (42 U.S.C. 262)) and because the regulation of all biologics for human use is now the responsibility of FDA. Thus, the statutory language of the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and regulations promulgated under each act clearly regulate the manufacturing practice of biologics, including whole blood, red blood cells, and allergenic products. Therefore, the Commissioner proposes to revoke § 229.25.

The Commissioner intends that the regulations proposed in Parts 201, 207, 210, and 211 shall become effective 6 months after the date of publication of the final regulation in the FEDERAL REGISTER. The proposal, as it applies to Part 229, would become effective 30 days after the date of publication of the final regulation in the FEDERAL REGISTER.

The Commissioner advises that publication of this proposal to revise the CGMP regulations in no way affects the applicability or eneforcement of those CGMP regulations presently in effect under Parts 210 and 211 (21 CFR Parts 210 and 211). The Commissioner particularly advises that the regulation on asbestos-form particles in drugs for parenteral injection, published in the FEDERAL REGISTER of March 14, 1975 (40 FR 11865), remains in full force and effect, and that the compliance dates stated therein remain unchanged.

The Commissioner has carefully considered the inflation impact of the proposed regulation and no major inflation impact has been found, as defined in Executive Order 11821, OMB Circular A-107, and interim guidelines issued April 1, 1975 by the Department of Health, Education, and Welfare. A copy of the FDA inflation impact assessment and other pertinent background data on which the Commissioner relies in proposing this regulation is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 501, 502, 505, 506, 507, 510, 701, 52 Stat. 1049–1052 as amended, 1055–1056 as amended, 76 Stat. 794 as amended (21 U.S.C. 351, 352, 355, 356, 357, 360, 371)) and the Drug Listing Act of 1972 (Pub. L. 92–387; 86 Stat. 559–562) and under the authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes that Parts 201, 207, 210, 211, and 229 be amended as follows:

PART 201—LABELING

1. By revising § 201.17 in Part 201 to read as follows:

§ 201.17 Drugs; location of expiration date.

The expiration date of a drug product, required by § 211.137 of this chapter, shall appear on the immediate drug product container, the outer retail package labeling, and the shipping carton. However, when single-dose containers are packed in individual cartons, the expiration date may properly appear on the individual carton instead of the immediate product container.

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

2. By revising paragraph (b) and adding a new paragraph (k) in § 207.3 in Part 207 to read as follows:

§ 207.3 Definitions.

* * * * *

(b) "Establishment" means a place of business under one management at one general physical location. The term includes, among others, independent laboratories that engage in control activities for registered drug establishments, e.g., "consulting" laboratories, manufacturers of medicated feeds and of vitamin products that are "drugs" within the meaning of section 201(g) of the act, human blood donor centers, animal facilities used for the production or control testing of licensed biologicals, and establishments engaged in the salvaging of drug products.

* * * * *

(k) "Drug product salvaging" is the act of segregating drug products that may have been subjected to prolonged or improper storage or to abnormal environmental conditions such as extremes of temperature, humidity, smoke, fumes, pressure, age, or radiation for the purpose of returning some or all of the products to the marketplace.

§ 207.20 [Amended]

3. By amending § 207.20 in Subpart B of Part 207 by adding a comma and the phrase "nor is drug listing required for establishments engaged in the salvaging of drug products" before the period at the end of paragraph (a).

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS: GENERAL

4. By revising Part 210 to read as follows:

Sec.
210.1 Status of current good manufacturing practice regulations.
210.2 Applicability of current good manufacturing practice regulations.
210.3 Definitions.

AUTHORITY: Secs. 501, 701, 52 Stat. 1049–1050 as amended, 1055–1056 as amended (21 U.S.C. 351, 371).

§ 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in Parts 210 through 229 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug product to assure that such drug product meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in Parts 210 through 229 of this chapter in the manufacture, processing, packing, or holding of a drug product shall render such drug product to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

§ 210.2 Applicability of current good manufacturing practice regulations.

The regulations in this part and in Parts 211 through 229 of this chapter as they may pertain to drug products, and in Parts 600 through 680 of this chapter as they may pertain to biological drug products, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug product in question shall supersede the more general.

§ 210.3 Definitions.

(a) The following definitions of terms apply to Parts 210 through 229 of this chapter.

(b) The terms are as follows:

(1) "Act" means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301).

(2) "Batch" means a specific quantity of a drug that has uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) "Component" means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

(4) "Drug product" means a finished dosage form, e.g., tablet, capsule, solution, etc., that contains the active drug ingredient generally, but not necessarily, in association with inactive ingredients.

(5) "Fiber" means any particle with a length at least three times greater than its width.

(6) "Non-fiber-releasing filter" means any filter, which after any apropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos or glass fibers are deemed to be fiber-releasing filters.

(7) "Active ingredient" means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of diseases, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

(8) "Inactive ingredient" means any ingredient other than an "active ingredient" present in a drug product.

(9) "In-process materials" include any materials fabricated, compounded, blended or derived by chemical reaction that are subsequently used in the preparation of the drug product.

(10) "Lot" means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

(11) "Lot number, control number, or batch number" means any distinctive combination of letters or numbers, or both, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product can be determined.

(12) "Manufacture, processing, packing, or holding of a drug product" includes packaging and labeling operations, testing, and quality control of drug products.

(13) "Medicated feed" means any "complete feed," "feed additive supplement," or "feed additive concentrate" as defined in § 121.200 of this chapter and is a feed that contains one or more drugs as defined in section 201(g) of the act. Medicated feeds are subject to Part 225 of this chapter.

(14) "Medicated premix" means a substance that meets the definition in § 121.200 of this chapter for a "feed additive premix," except that it contains one or more drugs as defined in section 201(g) of the act and is intended for manufacturing use in the production of a medicated feed. Medicated premixes are subject to Part 226 of this chapter.

(15) "Quality control unit" means any person or organizational element designated by the firm to perform the duties relating to quality control.

(16) "Strength" means:

(i) The concentration of the drug substance (e.g., weight/weight, weight/volume, or unit dose/volume basis), and/or

(ii) The potency, i.e., the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

(17) "Theoretical yield" means the quantity that would be produced at any stage of manufacture, processing or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

(18) "Actual yield" means the quantity that is actually produced at any stage of manufacture, processing, or packing of a particular drug product.

(19) "Percentage of theoretical yield" means the ratio of the actual yield (at any stage of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same stage), stated as a percentage.

(20) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in the regulations in Parts 210 through 229 of this chapter.

(21) "Acceptance criteria" means the product specifications and the associated sampling plan that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

(22) "Acceptable quality level (AQL)" means, in a sampling plan, the highest percent of defective units for each appropriate product characteristic that is acceptable as a process average. It is the lot or batch quality level associated with a high probability of acceptance, usually 95 percent.

(23) "Unacceptable quality level (UQL)" means, in a sampling plan, that percent of defective units for which there is a defined low probability of acceptance for a lot or batch. The term UQL is synonymous with the trade term Lot Tolerance Percent Defective (LTPD).

(24) "Representative sample" means a sample that consists of a number of units drawn at random from each part of a lot or batch to assure that the sample accurately represents the lot or batch.

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR DRUG PRODUCTS

5. By revising Part 211 to read as follows:

Subpart A—General Provisions

Sec.
211.1 Scope of Part 211.
211.2 Drug products, manufacturing practice.
211.3 Definitions.

Subpart B—Organization and Personnel

211.22 Responsibility of quality control unit.
211.25 Personnel qualifications.
211.28 Personnel responsibilities.
211.34 Consultants.

Subpart C—Buildings and Facilities

211.42 Design and construction features.
211.44 Lighting.
211.46 Ventilation, air filtration, air heating and cooling.
211.48 Plumbing.
211.50 Sewage and refuse.
211.52 Washing and toilet facilities.
211.54 Animal facilities.
211.56 Sanitation.
211.58 Maintenance.

Subpart D—Equipment

211.63 Equipment design, size, and location.
211.65 Equipment construction.
211.67 Equipment cleaning and maintenance.
211.68 Equipment calibration.
211.72 Filters.

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AUTHORITY: Secs. 501, 701, 52 Stat. 1049–1050 as amended, 1055–1056 as amended (21 U.S.C. 351, 371).

Subpart A—General Provisions

§ 211.1 Scope of Part 211.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of any drug product for administration to humans or animals.

(b) The current good manufacturing practice regulations in Subchapter C of this chapter, as they pertain to drug products, and in Parts 600 through 680 of this chapter, as they pertain to biological drug products, shall be considered to supplement, not supersede, the regulations in this part unless the regulations explicitly provide otherwise. In the event it is impossible to comply with applicable regulations both in this part and in other parts of Subchapter C of this chapter or in Parts 600 through 680 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the regulation in this part.

§ 211.2 Drug products; manufacturing practice.

(a) The regulations in this part permit the use of precision automatic, mechanical, or electronic equipment in the manufacture, processing, packing, and holding of drug products.

(b) Use of computers in the manufacture, processing, packing, and holding of drug products is also permitted. Appropriate controls shall be exercised over computer operations to assure that changes in master production and control records or other records are instituted only by authorized personnel. Reproductions of formulas or other records or data from the computer shall be checked for accuracy. A backup file of hard copy data entered into the computer shall be maintained except where certain hard copy, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard data to be retained in case of accidental erasure of the information stored in a computer shall include:

(1) Master formulas;

(2) Specifications;

(3) Test data;

(4) Other master production or control records;

(5) Batch production or control records, or programs for calculations.

§ 211.3 Definitions.

The definitions set forth in § 210.3 of this chapter apply in this part.

Subpart B—Organization and Personnel

§ 211.22 Responsibilities of quality control unit.

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality contol unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products (e.g., determining compliance with a bioequivalence standard) shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing.

§ 211.25 Personnel qualifications.

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practices (including the current good manufacturing practice regulations in Subchapter C of this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted on a continuing basis by well-qualified individuals.

(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

(c) There shall be an adequate number of personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

§ 211.28 Personnel responsibilities.

(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. They shall wear appropriate head coverings, as necessary, including facial hair coverings, to prevent contamination of drug products. Their arms and hands shall be covered when necessary to protect the drug product being handled.

(b) Employees shall practice good sanitation and health habits.

(c) Only authorized personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected. All employees shall be instructed to report to supervisory personnel any conditions that they consider may have an adverse effect on drug products.

§ 211.34 Consultants.

Consultants shall have sufficient education and experience to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C—Buildings and Facilities

§ 211.42 Design and construction features.

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to eliminate unnecessary traffic, particularly movement back through areas in which these materials had previously been processed or held.

(c) Operations shall be performed within specifically defined areas of adequate size. To prevent contamination or mixups, there shall be separate or defined areas for:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

(2) Holding rejected components, drug product containers, closures and labeling before disposition to prevent their use in operations for which they are unsuitable;

(3) Storage of released components, drug product containers, closures, and labeling;

(4) Storage of in-process materials;

(5) Any manufacturing and processing operations;

(6) Any packaging and labeling operations;

(7) Quarantine storage before release of drug products;

(8) Storage of drug products after release;

(9) Control and laboratory operations;

(10) Aseptic processing, when appropriate, which includes:

(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;

(ii) Temperature and humidity controls;

(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;

(iv) A system for monitoring environmental conditions;

(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;

(vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Penicillin production operations shall be performed in facilities separate from those used for other drug products.

§ 211.44 Lighting.

Adequate lighting shall be provided in all areas.

§ 211.46 Ventilation, air filtration, air heating and cooling.

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when necessary for the manufacture, processing, packing, or holding of a drug product.

(c) Air filtration systems, including prefilters and appropriate particulate matter air filters, shall be used on air supplies to production areas. If air is recirculated to production areas, appropriate filtration shall be used to prevent recirculation of dust from production. In areas where air contamination occurs during production, there shall be a system to provide frequent air changes with exhaust to the outside of the building.

(d) There shall be exhaust systems adjacent to dusty operations to remove dust.

(e) Air-handling systems for penicillin production shall be completely separate from those for other drug products.

§ 211.48 Plumbing.

(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Public Health Service Drinking Water Standards set forth in Subpart J of 42 CFR Part 72. Water not meeting such standards shall not be permitted in the plumbing system.

(b) Drains shall be of adequate size and, where connected directly to a sewer, shall be equipped with traps to prevent back-siphonage.

§ 211.50 Sewage and refuse.

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

§ 211.52 Washing and toilet facilities.

Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

§ 211.54 Animal facilities.

There shall be suitable housing and space for the care of laboratory animals.

§ 211.56 Sanitation.

(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition. Any such building shall be kept free of rodents, birds, insects, and other vermin, (other than laboratory animals), and of trash and decaying organic matter.

(b) There shall be written procedures assigning responsibility for sanitation and describing in detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

(c) Rodenticides, insecticides, fungicides, fumigating agents, and other cleaning and sanitizing materials shall be used only if the person engaged in the manufacture, processing, packing, or holding of a drug product has evidence that use of such materials will not contaminate equipment, components, drug product containers, closures, packaging or labeling materials, in-process materials, or drug products. Rodenticides, insecticides, and fungicides shall not be used unless registered in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

(d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

§ 211.58 Maintenance.

Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

Subpart D—Equipment

§ 211.63 Equipment design, size, and location.

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitable location to facilitate operations for its intended use as well as for its cleaning and maintenance.

§ 211.65 Equipment construction.

(a) Equipment shall be constructed so that surfaces coming into contact with drug products or in-process materials shall not be reactive, additive, or absorptive.

(b) Any substances required for operation such as lubricants or coolants, shall not come into contact with drug components drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product.

§ 211.67 Equipment cleaning and maintenance.

(a) Equipment shall be cleaned and maintained regularly to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product.

(b) There shall be written procedures assigning responsibility for cleaning and maintenance and describing in detail the maintenance and cleaning schedules, the methods, equipment and materials to be used and the methods of disassembling and reassembling, for all equipment used in the manufacture, processing, packing, or holding of a drug product; such written procedures shall be followed.

(c) Records shall be kept of maintenance and cleaning operations, as specified in § 211.182.

§ 211.68 Equipment calibration.

(a) When precision automatic, mechanical, or electronic equipment is used in the manufacture, processing, packing, and holding of a drug product, it shall be routinely calibrated, inspected, or checked according to a written program that assures proper performance. Written records of those calibration checks and inspections shall be maintained.

(b) Scales and balances used for testing or production operations shall be accurate. Calibration checks shall be made at least once every 6 months and written records of those calibration checks shall be maintained.

§ 211.72 Filters.

(a) Filters used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these drug products unless it is not possible to manufacture such drug products without the use of such a filter.

(b) If use of a fiber-releasing filter is necessary, an additional non-fiber-releasing filter of 0.22 micron maximum mean porosity (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the drug product. Use of an asbestos-containing filter, with or without subsequent use of a specific non-fiber-releasing filter, is permissible only upon submission of proof to the appropriate bureau of the Food and Drug Administration that use of a non-fiber-re-

leasing filter will, or is likely to, compromise the safety or effectiveness of the drug product.

(c) Substitution for a fiber-releasing filter shall be achieved on or before September 14, 1976. If such substitution is not achieved on or before March 14, 1976, manufacturers shall submit monthly progress reports to the appropriate bureau of the Food and Drug Administration. Such substitution shall be shown to have been effected without loss of safety or effectiveness of the drug product.

Subpart E—Control of Components, Drug Product Containers, Closures, and In-process Materials

§ 211.80 General requirements.

(a) There shall be written procedures describing in detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components, drug product containers, and closures; such written procedures shall be followed.

(b) Components, drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination of, or by, other components, in-process materials, or drug products.

(c) Bagged and boxed components, drug product containers, or closures shall be stored on pallets or free-standing shelves off the floor and at least 2 feet away from walls.

(d) Each container of components, drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected) and as to whether (and when) it has been opened and sampled.

§ 211.82 Receipt and storage of untested components, drug product containers, and closures.

(a) Upon receipt and before acceptance, each container of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested and released. Storage within the area shall conform to the requirements of § 211.80.

§ 211.84 Testing and approval or rejection of components, drug product containers, and closures.

(a) Each lot of components, drug product containers, and closures shall be withheld from use until their containers have been identified and the lot sampled, tested, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate statistical criteria (such as component variability, confidence levels, and degree of precision desired), the past quality history of the supplier, and the quantity needed for analysis and reserve.

(c) Samples shall be collected in accordance with the following procedures:

(1) The containers of components selected shall be cleaned by wiping or vacuuming.

(2) The containers shall be opened, sampled, and resealed in a suitable area where there is no potential for contamination of other containers of components, drug product containers, or closures.

(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.

(4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.

(5) Sample containers shall be identified with the name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name and signature of the person who collected the sample.

(6) Containers from which samples are taken shall be carefully closed to prevent contamination or deterioration.

(d) Samples shall be examined and tested as follows:

(1) At least one identity test shall be conducted that is specific for each active and inactive ingredient.

(2) Each active and inactive ingredient shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a complete report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate validation of the supplier's test results.

(3) When appropriate, components shall be microscopically examined.

(4) Any component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined for such contamination. Any such lot of components, drug product containers, or closures that does not meet established specifications shall be rejected.

(5) Any component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use. Any such lot of components, drug product containers, or closures that contain microorganisms that are objectionable in view of its intended use shall be rejected.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any such material that does not meet such specifications shall be rejected.

§ 211.86 Use of approved components, drug product containers, and closures.

Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first.

§ 211.87 Retesting of approved components, drug product containers, and closures.

Components, drug product containers, and closures shall be retested for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with § 211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might affect the component, drug product container, or closure.

§ 211.88 Testing of in-process materials.

In-process materials shall be tested for identity, strength, quality, and purity and approved or rejected by the quality control unit, pursuant to procedures in § 211.84, as appropriate during the production process, e.g., at commencement or completion of significant stages, or after storage for long periods.

§ 211.89 Rejected components, drug product containers, closures, and in-process materials.

Rejected components, drug product containers, closures, and in-process materials shall be identified and quarantined to prevent their use in manufacturing or processing operations for which they are unsuitable.

§ 211.94 Drug product containers and closures.

(a) Containers for the holding of a drug product, including closure systems, shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

(b) Container closure systems shall provide adequate protection against external factors in storage and use that can cause deterioration or contamination of the drug product.

(c) Containers for the holding of a drug product, including closure systems, shall be cleaned and, where indicated by the nature of the drug, sterilized and depyrogenated to assure that they are suitable for their intended use. Containers for injectable drug products intended for human use, or components of such products, shall be cleansed with water that has been filtered through a nonfiber-releasing filter equivalent to that indicated in § 211.72.

(d) Procedures, standards or specifications, and methods for testing, cleaning, sterilizing and depyrogenating containers, closure systems, and other parts shall be written and followed.

(e) Containers, closure systems, and other parts that do not comply with the requirements of paragraphs (a) through (d) of this section shall not be used for the holding of a drug product.

§ 211.96 Documentation of controls.

Records shall be maintained for each shipment received of components, drug product containers, and closures indicating receipt, sampling, testing, or examination and disposition (including dates and personnel involved), as specified in § 211.184.

Subpart F—Production and Process Controls

§ 211.100 Written procedures; deviations.

(a) There shall be written procedures for manufacturing and quality control to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted and approved by the appropriate organizational unit and reviewed and approved by the quality control unit.

(b) Written manufacturing and quality control procedures shall be followed in the execution of the various manufacturing and quality control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

§ 211.101 Charge-in of components.

Written production and control procedures shall include the following to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess:

(a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled amount of active ingredient.

(b) Components shall be subdivided, weighed, or measured before dispensing to manufacturing. If a component is removed from the original container to another, the new container shall be identified with the following information:

(1) Component name or item code;

(2) Receiving or control number;

(3) Weight or measure in new container;

(4) Batch for which component was dispensed, including product name, strength, and lot number.

(c) Weighing, measuring, or subdividing operations for components shall be closely supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

(1) The component was released by the quality control unit;

(2) The weight or measure is correct as stated in the batch production records;

(3) The containers are properly indentified.

(d) Each component shall be added to the batch by one person and verified by a second person.

§ 211.102 Manufacturing instructions.

The manufacturing instructions in the batch production records shall be strictly followed.

§ 211.103 Calculation of yield.

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each distinct phase of manufacturing, processing, packaging or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.

§ 211.105 Equipment identification.

(a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to accurately indicate their contents and, when necessary, the stage of processing of the batch.

(b) Each major piece of equipment shall bear a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product.

§ 211.110 Sampling of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following:

(1) Tablet or capsule weight variation;

(2) Disintegration time;

(3) Adequacy of mixing to assure uniformity and homogeneity;

(4) Dissolution time and rate, where appropriate;

(5) Clarity, completeness, or pH of solutions.

(b) Valid in-process specifications for such characteristics shall be consistent with finished drug product specifications and shall be derived from previous acceptable process average and process variability estimates determined by the application of suitable statistical procedures. Examination and testing of samples shall assure that the drug product and in-process material conform to process average and variability requirements established by in-process specifications. In-process sampling, examination, and testing shall be conducted in accordance with written procedures.

§ 211.111 Time limitations on production.

When appropriate, time limits for the completion of each stage of production shall be established to assure the quality of the drug product.

§ 211.112 Sanitation of equipment.

(a) Written procedures shall be established and followed for cleaning and/or sanitizing all equipment, utensils, and containers to prevent contamination and mixups. These procedures shall include, but are not necessarily limited to, the following:

(1) Removal or obliteration of previous batch identification;

(2) Method of cleaning and the agents and equipment to be employed;

(3) Cleaning and/or sanitizing schedules;

(4) Protection of cleaned articles or facilities from contamination prior to use;

(5) Inspection of articles and facilities for cleanliness immediately before use;

(6) Documentation of cleaning, sanitizing, and inspection as specified in §§ 211.180 and 211.182.

(b) Appropriate written procedures shall be established and followed prescribing precautions designed to prevent cross-contamination of drug products during manufacturing and storage.

§ 211.113 Prevention of microbiological contamination.

(a) Appropriate written procedures shall be established and followed prescribing precautons to be taken to prevent the presence of objectionable microorganisms in drug products not required to be sterile.

(b) Appropriate written procedures shall be established and followed prescribing precautions to prevent microbiological contamination in the production of drug products purporting to be sterile. These precautions shall include validation of any sterilizing process.

§ 211.115 Reprocessing.

(a) A written procedure shall be established and followed prescribing the handling of batches that do not conform to standards or specifications and the steps to be taken to ensure that, if they are reprocessed, the reprocessed batches will conform with all established standards, specifications, and characteristics.

(b) Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G—Packaging and Labeling Control

§ 211.122 Materials examination and usage criteria.

(a) There shall be written procedures describing in detail the receipt, identification, storage, handling, examination and/or testing of labeling and packaging materials; such written procedures shall

be followed. All labeling and packaging materials shall, upon receipt and before use in packaging or labeling of a drug product, be examined or tested and approved or rejected by the quality control unit.

(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and disposition (including dates and personnel involved), as specified in § 211.184.

(d) Labeling and other packaging materials for each different drug product, strength, dosage form, or quantity of contents shall be stored in separate compartments with suitable identification. Access to the storage area shall be limited to authorized personnel only.

(e) Rejected and outdated labels, labeling, and other packaging materials shall be destroyed.

(f) Gang printing of labeling to be used for different drug products or different strengths of the same drug product (or labeling of the same size and identical or similar format and/or color schemes) shall be minimized. If gang printing is employed, packaging and labeling operations shall provide for special control procedures, taking into consideration sheet layout, stacking, cutting, and handling during and after printing.

(g) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record. Any excess printed drug product containers, labels, or labeling bearing lot or control numbers shall be destroyed.

§ 211.125 Labeling issuance.

(a) Strict control shall be exercised over labeling issued for use in drug product labeling operations.

(b) Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master production records.

(c) Control procedures shall be utilized to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of any discrepancies found between the quantity of drug product finished and the quantity of labeling issued.

(d) All excess labeling bearing lot or control numbers shall be destroyed.

(e) Returned labeling shall be maintained and stored in a manner to prevent mixups and provide proper identification.

(f) Any significant unexplained discrepancy shall be investigated in accordance with § 211.192.

(g) Procedures shall be written describing in detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

§ 211.130 Packaging and labeling operations.

There shall be written procedures that specify packaging and labeling operations to assure that correct labels, labeling, and packaging materials are used for the drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and cross-contamination by a physical separation from operations on other drugs;

(b) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(c) Examination of packaging and labeling materials for correctness before packaging operations, and documentation of such examination in the batch production record.

(d) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products and previously used packaging and labeling materials have been removed. Written results of the inspection shall be documented in the batch production records.

(e) Removal of packaging and labeling materials from the finishing area after completion of operations and prior to starting the next run.

§ 211.134 Drug product inspection.

(a) Packaged and labeled products shall be examined during finishing operations to assure that every container and package in the lot has the correct label.

(b) A representative sample of units selected at random shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.

(c) Results of these examinations shall be recorded in the batch production records.

§ 211.137 Expiration dating.

(a) To assure that a drug product meets appropriate standards of identity, strength, quality, and purity at the time of use, it shall bear a statistically validated expiration date determined by appropriate stability tests.

(b) Expiration dates appearing on the drug labeling shall be supported by appropriate statistical analysis of readily available data from stability studies described in § 211.166.

(c) Expiration dates shall be related to appropriate storage conditions stated on the labeling, as determined by stability studies described in § 211.166.

(d) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.

(e) Expiration dates shall appear on labeling in accordance with the requirements of § 201.17 of this chapter.

Subpart H—Holding and Distribution

§ 211.142 Warehousing procedures.

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

(a) Quarantine of drug products before release by the quality control unit.

(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

§ 211.150 Distribution procedures.

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first whenever possible.

(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Subpart I—Laboratory Controls

§ 211.160 General requirements.

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. These requirements shall be followed in the execution of the various laboratory control functions and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

(4) The calibration of instruments, apparatus, gages, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met.

§ 211.165 Testing and release for marketing.

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to all appropriate finished drug product specifications, including the identity and strength of each active ingredient, prior to release.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in a written procedure that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release.

(1) The statistical quality control criteria shall include an appropriate Acceptable Quality Level (AQL) and an appropriate Unacceptable Quality Level (UQL) that shall be assigned to percents of defective units for drug product specifications that require multiple examination or testing of individual dosage units to determine if the product meets its specifications (e.g., content uniformity, weight variation, dissolution, etc.) based on the significance of the defect. The determination of conformance to appropriate specifications and statistical quality control criteria for those product quality characteristics requiring multiple testing or examination may be satisfied through the utilization of drug product testing, statistical quality control data developed and recorded during the processing of the batch, and statistical data derived from validation studies conducted to determine the variability of the manufacturing processes.

(2) When a maximum allowable percent of defective units for a quality control specification is indicated, such as a new drug application commitment or as an official compendial requirement, this allowable maximum percent of defective units for this characteristic, expressed as a percentage (i.e., the maximum allowable number of defectives of a specified characteristic in a sample divided by the number of units in the sample multiplied by 100), shall be considered as the maximum UQL for the quality characteristic tested. Quality control procedures shall ensure that there is no greater than a 5 percent probability of acceptance of batches whose percentage of defective units exceeds the UQL for that particular quality characteristic. The establishment of AQL's and UQL's is not suitable in the design of all sampling plans for characteristics such as sterility or pyrogenicity of drugs since the number of tests and examinations required to satisfy a UQL of 0 percent defective would require destructive testing of every unit in the batch.

(e) The accuracy, sensitivity, specificity, and reproducibility of tests methods employed by the firm shall be established and documented.

(f) Laboratory reference standards shall be properly stored and tested to assure their conformance to appropriate specifications. They shall be identified as to source, lot, or other similar reference number, date of receipt, and last date of testing. They shall be retested, as necessary, to assure that they remain suitable for use.

(g) Components, drug product containers, closures, in-process materials, labeling, or drug products failing to meet established standards or specifications and statistical and any other relevant quality control criteria, shall be rejected. Reprocessing may be performed provided there is assurance that the reprocessed material will meet appropriate standards, specifications, and characteristics.

§ 211.166 Stability testing.

(a) There shall be a written testing program designed to assess the stability characteristics of drug products and used to establish storage conditions and expiration dates; such program shall be followed. It shall include:

(1) Statistical criteria, including sample size and test intervals, for each attribute examined to assure statistically valid estimates of stability;

(2) Storage conditions for samples tested;

(3) Reliable, meaningful, and specific test methods;

(4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;

(5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided adequate shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

§ 211.167 Special testing requirements.

(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.

(b) For each batch of ophthalmic ointments, there shall be appropriate laboratory testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

(c) For each batch of controlled-release dosage forms, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

§ 211.170 Reserve samples.

(a) An appropriately identified reserve sample selected at random from each lot in each shipment of each component shall be retained for at least 2 years after the expiration date of the last lot of the drug product containing the component. It shall consist of at least twice the quantity necessary for all tests required to determine whether the component meets its established specifications, except those for sterility and pyrogens. Samples of components that do not appear in the finished dosage form, such as solvents, compressed gases, and water, need not be retained.

(b) A properly identified reserve sample of units selected at random from each lot or batch of drug product shall be stored under conditions consistent with product labeling and shall be retained for at least 2 years after the expiration date of the drug product. The sample shall be stored in the same immediate container-closure system in which the drug is marketed and shall consist of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Such samples shall be inspected annually for evidence of deterioration and the results shall be recorded and maintained with other stability data on the drug product.

§ 211.173 Laboratory animals.

Animals used in testing a component, in-process material, or drug product for compliance with its established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

§ 211.176 Penicillin contamination.

If the possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such product shall not be marketed if de-

tectable levels are found when tested according to procedures specified in "Procedures for Detecting and Measuring Penicillin Contamination in Drugs." [1] Division of Antibiotics and Insulin Certification, Food and Drug Administration, Washington, DC 20204, October 1965.

Subpart J—Records and Reports

§ 211.180 General requirements.

(a) Any production, control, or distribution record that is maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 2 years after the expiration date of the batch.

(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 2 years after the expiration date of the last lot of drug product incorporating the component or using the container, closure, or labeling.

(c) All records, or copies of records, shall be readily available for inspection during the retention period at the establishment where the activities described in such records occurred.

(d) Written records required by this part shall be maintained so that data therein can be used to produce a written summary covering every batch for each drug product. These summaries shall be prepared and maintained to provide the capability for review on a product-by-product basis so that a profile can be established for each drug product to assist in the updating of quality standards.

(1) Summaries described in this paragraph shall be prepared and evaluated on at least an annual basis and shall be retained for at least 2 years after the expiration date of the last batch of drug product manufactured, whether or not the batch was accepted, rejected, offered for sale, or distributed.

(2) The written summaries and evaluations shall be available for review during establishment inspections.

(e) Procedures shall be established to assure that the responsible corporate officials of the firm are notified in writing of any investigations conducted under §§ 211.198, 211.204, or 211.208 of these regulations, of any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration. These procedures shall specify, among other things, that a routine written report shall be issued at least quarterly summarizing all such matters and the status of corporate actions being taken to resolve outstanding problems.

§ 211.182 Equipment cleaning and use log.

A written record of equipment cleaning, maintenance, and use shall be included in individual equipment logs that show the date, time, product, strength, and lot number of each batch processed. The persons performing and double-checking the cleaning and maintenance shall date and sign the log indicating the work performed. Entries in the log shall be in chronological order.

§ 211.184 Component, drug product, container, closure, and labeling records.

These records shall include the following:

(a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s); the receiving code as specified in § 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.

(b) The results of any test or examination performed (including those performed as required by § 211.82(a), § 211.84(d), or § 211.122(a)) and the conclusions derived therefrom.

(c) An individual inventory record, including reconciliation of the use of each lot of each component, drug product container, and closure.

(d) Documentation of all inspection and review of labels and labeling for conformity with established specifications.

§ 211.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Such records shall include:

(1) The name and strength of the product and a description of the dosage form;

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure, using the same weight system (metric, avoirdupois, or apothecary) of each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;

(6) A statement of theoretical weight or measure at various stages of processing;

(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to § 211.192 is required;

(8) A description of the drug product containers, closures, and packaging and finishing materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

§ 211.188 Batch production and control records.

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

(a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;

(b) Proof that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:

(1) Dates;

(2) Identity of individual major equipment and lines used;

(3) Specific identification of each batch of component or in-process material used;

(4) Weights and measures of components used in the course of processing;

(5) In-process and laboratory control results;

(6) Inspection of the packaging and labeling area before and after use;

(7) A statement of percentage of theoretical yield at all major stages of processing;

(8) Complete labeling control records, including specimens of all labeling used;

(9) Description of drug product containers and closures;

(10) Any sampling performed;

(11) Identification of the persons performing and supervising each significant step in the operation;

(12) Any investigation made according to § 211.192.

(13) Results of examinations made in accordance with § 211.134.

§ 211.192 Production record review.

All production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure or a batch or any of its components to meet any of its specifications shall be thoroughly investigated whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the spe-

[1] Copies may be obtained from: Director, NCAA (HFD-430), Food and Drug Administration, 200 "C" St., SW., Washington, DC 20204.

cific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup.

§ 211.194 Laboratory records.

(a) Laboratory records shall include complete data derived from all tests, examinations, and assays as follows:

(1) A description of the sample received for analysis or testing with identification of source, quantity, lot number, and date of receipt.

(2) A statement of each analytical method used in the analysis of the sample. The statement shall indicate the location of data from the tests to show that the methods used in the analysis of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the "United States Pharmacopeia," National Formulary," "Association of Official Analytical Chemists, Book of Methods," [2] or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all analytical methods used for control purposes must be verified under actual conditions of use.

(3) A statement of the weight or measure of sample taken for each analysis or test.

(4) A full record of all data secured in the course of each assay examination or test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.

(5) A record of all calculations performed in connection with the analysis, including units of measure, conversion factors, and equivalency factors.

(6) A full description of any modifications of established methods employed in the analysis of the sample, together with the reason therefor and data to show that the modification produces results that are accurate and reliable for the material examined.

(7) A statement of the results of analysis and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, inprocess material, or drug product tested.

(8) The signature of the person who performs each assay or test and the date(s) the tests were performed.

(9) The endorsement of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

(b) Complete records shall be maintained of the testing and standardization of laboratory reference standards required by § 211.165(g).

[2] Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, D.C. 20044.

(c) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 211.160(b).

(d) Complete records shall be maintained of all stability testing performed on all components, in-process materials, and drug products.

§ 211.196 Distribution records.

Distribution records shall contain the name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.

§ 211.198 Complaint files.

(a) All written and oral complaints regarding a drug product shall be reviewed by the quality control unit and a determination made as to whether or not an investigation is necessary. Any complaint involving the possible failure of a drug product to meet any of its specifications shall be investigated in accordance with § 211.192.

(b) A written record of each complaint and investigation shall be maintained in a file designated for drug product complaints. The written record shall include the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant. Where an investigation is made, the record shall include the findings of the investigation and followup. Where no investigation is made, the record shall include the reason that an investigation was unnecessary and the name of the responsible person making such a determination. The record shall be maintained for at least 2 years after the expiration date of the drug product. Companies that have more than one establishment shall maintain a copy of each complaint record at the establishment where the drug product involved was manufactured, processed, or packed (but not necessarily at every establishment where held only).

Subpart K—Returned and Salvaged Drug Products

§ 211.204 Returned drug products.

Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, cast doubt on the safety, identity, strength, quality, or purity of the drug product or its bioavailability, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. If the drug product is not destroyed, it may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of § 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

§ 211.208 Drug products salvaging.

Drug products that have been subjected to prolonged or improper storage or to abnormal environmental conditions such as extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question that drug products may have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug product meets all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to prolonged or improper storage or abnormal environmental conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products have maintained their original identity, strength, quality, and purity.

PART 229—CURRENT GOOD MANUFACTURING PRACTICE FOR CERTAIN OTHER DRUG PRODUCTS

§ 229.25 [Revoked]

6. By revoking § 229.25.

Interested persons may, on or before June 14, 1976, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal. Received comments may be seen in the above office during working hours, Monday through Friday. Ordinarily 60 days is provided for comment on a proposal, although the Commissioner can reduce or extend this time period for good cause. Because of the nature and extent of revisions being proposed, the Commissioner has concluded that 120 days should be allowed for public comment. In the absence of extraordinary circumstances, no extension of time for comment will be granted.

NOTE: It is hereby certified that the economic and inflationary effects of this proposal have been carefully evaluated in accordance with Executive Order No. 11821.

Dated: February 3, 1976.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.76-4113 Filed 2-12-76;8:45 am]